REMARKS

Status of the Claims

Claims 1-22, 31 and 39-54 were pending.

Claims 1-22, 31 and 39-54 have been rejected.

By way of this amendment, claims 9, 21 and 39-42 have been canceled, claims 1, 2, 4, 43 and 48 have been amended and new claims 55-60 have been added.

Upon entry of this amendment, claims 1-8, 10-20, 22, 31 and 43-60 will be pending.

Summary of the Amendment

Claims 32-38 were have been cancelled without prejudice previously. However, the earlier submitted amended claim set referred to them as being withdrawn. The claim set submitted herewith correctly refers to them as being canceled.

Claims 9, 21 and 39-42 have been canceled without prejudice.

Claims 1 has been amended to clearly indicate that the DNA that is administered is from the same species as the individual. Support for the amendment is found throughout the specification such as on page 3, lines 23-29 and page 5 line 28 to page 6 line 6. No new matter has been added.

Claims 2 and 4 have been amended to correct syntax and more clearly set forth embodiments of the invention. No new matter has been added.

Claim 43 has been amended to correct an obvious grammatical error and to indicate that the individual is human and that the donor DNA is human genomic DNA. Support for the amendment is found throughout the claims as filed and specification, particularly page 3, lines 23-25. No new matter has been added.

Claim 48 has been amended to indicate that the individual is human and that the donor DNA is human genomic DNA. Additionally, claim 48 has been amended to recite that the donor DNA is from an individual who does not have the disease or disorder associated with exposure to mutagenic stimuli. Support for the amendment is found throughout the claims as filed and specification, particularly page 12, lines 22-24. No new matter has been added.

New claims 55-60 are directed at specific embodiments of the invention. Support for the amendment is found in the claims as originally filed and throughout such as on pages 19 line 15 to page 20 line 3 and page 21 lines 16-27. No new matter has been added.

Objections

Claims 32-38 stand objected to because the reference to their cancellation in the earlier response did not include proper reference to their cancellation in the amended claim section of the response. The amended claim section of this response properly refers to claims 32-38 as canceled. Applicant respectfully requests that the objection be withdrawn.

Claims 43 and 48 stand objected to because the claims contain a grammatically error. As amended, the claims are grammatically correct. Applicant respectfully requests that the objection be withdrawn.

Rejection under 35 U.S.C. § 101 and 112

Claims 48-54 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. It is asserted that the claim does not contain support in the specification with respect to the source/nature of the donor DNA. Claims 48 has been amended to refer to the source and nature of the donor DNA as set forth in the specification.

Claims 48-54 are in compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. Applicant respectfully requests that the rejection of claims 48-54 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1-22, 31 and 39-42 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible asserted utility or a well-established utility. Applicant respectfully disagrees.

Claims 1-22, 31 and 39-42 stand rejected under 35 U.S.C § 112, first paragraph, because the claimed invention is allegedly not supported by either a credible asserted

utility or a well established utility and thus one skilled in the art would allegedly not know how to use the claimed invention.

The present invention represents such an improvement. On page 7 of the Official Action, the examiner mistakenly relies upon the "saturatability" of the DNA binding to cells as being a single event rather than a dynamic process which continues. The examiner mistakenly calculates that a single cell only binds to 3000 molecules of DNA. As noted above, the 3000 molecule figure is based upon the size of lambda DNA which is 48,500 bp. The claims indicate that the DNA to be administered is 100-3000 bp. Moreover, the calculations of the examiner are based upon a one-time, static process of binding rather than a continues process. One skilled in the art would not conclude from the teachings of Yanez, Porter and Riele that the utility is not credible. Rather, they would accept the utility as being credible.

On page 8 of the Official Action, the examiner dismissed the data in applicant's specification as lacking evidence of homologous recombination. The examiner refers to Gilchrist in support of this dismissal of Applicant's data. Gilchrist relates to the use of DNA fragment delivery to increase melanin production and discloses using salmon DNA to increase melanin production in a murine melanoma cell line. Nothing in Gilchrist suggests any reason to doubt the credibility of the utility of applicant's invention. One skilled in the art would conclude that the claimed invention has a credible utility and nothing in Gichrist suggests otherwise.

Ledoux (1965) is cited as reporting results from in vivo delivery of DNA to transform cells. Ledoux (1965) reports one successful report. None of the experiments, however, describe the experiments as delivering DNA according the present invention. The conclusions set forth in Ledoux (1965) are optimistic rather than doubtful. They clearly report that the reason why it was at the time uncertain whether DNA would be taken up by organs and tissue was not due to any contradictory data but rather because the studies were few and the results from those that existed were fragmentary. Ledoux (1965) reported that the primary concern, degradation of DNA in blood, turned out to be less of a problem than thought. One skilled in the art would consider the invention to have credible utility and nothing in Ledoux (1965) would lead them to conclude otherwise.

Beam (1959) is cited as reporting results form in vivo delivery of pigmented rat derived DNA into albino rats. The albino rats did not develop pigment nor did their off spring. The authors suggest possible reasons for the failure to produce a change in phenotype could have been destruction of the biological activity of the DNA by the method of preparation method, degradation of the DNA in vivo or low efficiency of transformation. The authors, however, do not indicate that in vivo transformation cannot work or that it is incredible to expect that it would.

Yoon (1964) is cited as reporting results form in vivo delivery of labeled exogenous homologous DNA into mice. The level of uptake of the DNA was reported to be less than level of spontaneous mutation. The authors suggest this low rate of uptake as the possible reasons for the failure to produce phenotype changes by in vivo delivery of DNA. The authors, however, do not indicate that in vivo transformation cannot work or that it is incredible to expect that it would.

Karpfel (1963) is cited as reporting that DNA is mutagenic and the level of mutagenesis is higher than that of homologous recombination. The reference reports the mutagenesis observed was caused by "a whole molecule of native DNA or its larger fragments." The data shows that level of mutagenesis is much higher when DNA from divergent species is used. The authors, however, do not indicate that in vivo transformation cannot work or that it is incredible to expect that it would.

Wilczok (1965) is cited as reporting that the benefits of systemic administration of DNA in the treatment of exposure to mutagenic stimuli was observed regardless of the source of DNA used. Ledoux (19170) is cited as supporting this conclusion. Importantly, the authors in both references do not indicate that in vivo transformation cannot work or that it is incredible to expect that it would. Rather, one skilled in the art would find the utility of the invention credible in view of disclosure in Wilczok.

Pfeiffer (1998) is cited as supporting an alternative theory for how administration of DNA has a protective effect on individuals exposed to mutagenic stimuli. There is no assertion that that in vivo transformation cannot work or that it is incredible to expect that it would. Rather, one skilled in the art would find the utility of the invention credible in view of disclosure in Pfeiffer.

Taube (2002) reports the case of chimeraplasty, its initial acceptance and subsequent dismissal as useful technology. The examiner cites this case history as supporting the assertion that those skilled in the art would not accept the utility of the current invention as credible. The article suggests otherwise. While stating that "many gene-therapy researchers expressed initial skepticism simply because the results were remarkable" the article actually describes the opposite reception of this technology. The article clearly chronicles that the developers of Chimeraplasty has there work published in prestigious peer reviewed journals. The authors received extensive research support in the form of peer reviewed government grants and the technology was the basis for starting a company that was able to attract a pioneer in gene therapy to lead it. Clearly, those of ordinary skill in the art completely embraced the technology as having a credible utility. While the story ends with a conclusion that the technology is not believed to be useful, the article clearly chronicles that the utility was credible and there is nothing suggesting that those skilled in the art would not consider other technology credible based upon the history of chimeraplasty.

The examiner has dismissed the Yakubov declaration filed under 37 CFR 1.132 with the previous response as insufficient. It is asserted that the experiments described in the declaration fail to provide unequivocal evidence that homologous recombination was responsible for the positive data. The examiner dismisses paragraph 5 of the declaration by arguing that the evidence provided in the instant Official Action prove that illegitimate recombination was more likely than homologous recombination. The position of the examiner is pure speculation and without merit.

These earlier experiments used a mixture of whole human genome DNA fragments for the repair of this mutation in the same MCF7 cells. Regarding paragraph 6, the examiner questions how the conditions of extended incubation in medium with DNA can be duplicated in vivo. The record clearly supports that DNA titers can be maintained. The specification clearly indicates that continuous or multiple administration can be used to maintain DNA levels. The Examiner also asserted that the results were similar in magnitude to those observed in gene targeting. Applicant notes that in a method that is reported in Yanez & Porter (1998), small fragment homologous replacement (SFHR), a much higher efficiency was demonstrated. By achieving such a

high efficiency the instant invention could circumvents some of the issues (e.g. insertional mutagenesis) that are strongly associated with viral cDNA-based methods. No detectable non-homologous insertions for small DNA fragments used in SFHR are found.

The Examiner also asserts that with so closely placed primers such as in the experiment described in the declaration it is impossible to say if the repaired gene or a relatively long DNA therapeutic fragment that just entered the cell nucleus was observed. However, the restoration of the apoptotic function (lost by cells as a result of the mutation) and acquisition by MCF7 cells of wild type-specific band covering the deletion region as major band in cells incubated with wild type (wt) human genomic fragments mixture comprising collectively entire set of human genomic sequences provides strong evidence in favor of the repair event.

The examiner cites Szybalska & Szybalski as evidencing the fact of repair of mutated gene using a wild type genomic DNA preparation and natural delivery techniques achieved an efficiency that was high for gene but not high enough for practical use. The short time of exposure could account for the low efficiency. In addition, the authors did not specified the molecular weight of the DNA used in the experiment which also effects efficiency.

The examiners assertion that the results in paragraph 6 could have been due to contamination is unfounded. The experiment was independently reproduced for four times with similar results.

The data provides overwhelming evidence of the ability of the current invention to repair a mutation in cellular genomic DNA.

The dismissal of the data in paragraphs 7-11 is improper. These data provide evidence in support of the operability of the claimed invention. These data demonstrate that the invention provides a therapeutic effect as claimed. Those skilled in the art would accept the utility as credible in view of the evidence of record.

When all of the evidence of record is considered in its totality, those skilled in the art would conclude that the claimed invention has a credible utility and that the specification enables those skilled in the art to use the claimed invention. As amended, the evidence of record supports the conclusion that the invention as claimed in amended claims 1-22, 31 have utility and is enabled. Applicant respectfully requests that the

rejections of claims 1-22 and 31 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 48-52 and 54 stand rejected under 35 U.S.C § 112, first paragraph, because while being enabled for treating an individual exposed to ionizing radiation, it is asserted that the specification does not enable methods for treating individuals exposed to other stimuli. It is asserted that specification does not enable one skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant respectfully disagrees.

It is well established that Applicant's assertions of enablement must be accepted as true unless the Examiner can present evidence or reasoning that would lead one skilled in the art to question the objective truth of the assertions. In this case, the Examiner has not met this burden and the totality of evidence on the record supports conclusion of enablement.

The Examiner questions the enablement of the embodiments not related to exposure to ionizing radiation. The evidence and reasoning presented is references are asserted to raise doubts as to the theorized mechanism stated in the specification. The specification indicates that Applicant was not limited to such a theory and the claims do not have any requirement that homologous recombination occurs. There is no requirement that an Applicant provide any explanation as to how the invention works and it is improper to reject a claim not limited to a mechanism of action because of asserted evidence that an unclaimed mechanism may be incorrect. The evidence and reasoning provided by the Examiner is not directed to the claimed invention. In fact, the totality of evidence of record strongly supports a finding of enablement. The examiner has not met the legal burden required to support an enablement rejection of claims 48-52 and 54.

The evidence of record overwhelming supports the conclusion that the invention as claimed in claims 48-52 and 54 is enabled. Applicant respectfully requests that the rejection of claims 48-52 and 54 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. § 102 and 103

Claims 43-53 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or under 35 U.S.C. § 103(a) as being obvious in view of Sekiguchi et al. (US 3,803,116). Sekiguchi et al. disclose a method of treating individuals who have cancer by administering fish sperm or mammalian organ DNA to such individuals. Sekiguchi et al. neither teaches or suggests using DNA containing essentially the entire human genome from an individual who does not have a disease or disorder with associated with exposure to mutagenic stimuli. Sekiguchi et al. neither teaches or suggests using such DNA as described in the claims. The examples in the reference specifically teach using DNA from a different species. When taken as a whole, one skilled in the art would not be motivated to use human DNA having essentially the entire human genome to treat a human.

Claims 43-53 are neither anticipated by Sekiguchi et al. nor obvious in view of it. Applicant respectfully requests that the rejection of claims 43-53 under 35 U.S.C. § 102(b) as being anticipated by or under 35 U.S.C. § 103(a) as being obvious in view of Sekiguchi et al. (US 3,803,116) be withdrawn.

Claims 43-53 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or under 35 U.S.C. § 103(a) as being obvious in view of Ledoux et al. Ledoux et al. disclose a method of treating irradiated mice by administering mouse DNA to them. Ledoux et al. neither teaches or suggests treating a human using DNA containing essentially the entire human genome from an individual who does not have a disease or disorder with associated with exposure to mutagenic stimuli. Ledoux et al. neither teaches or suggests using such DNA as described in the claims. When taken as a whole, one skilled in the art would not be motivated to use human DNA having essentially the entire human genome to treat a human.

Claims 43-53 are neither anticipated by Ledoux et al. nor obvious in view of it. Applicant respectfully requests that the rejection of claims 43-53 under 35 U.S.C. § 102(b) as being anticipated by or under 35 U.S.C. § 103(a) as being obvious in view of Ledoux et al. be withdrawn.

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(formerly PANA-0002)

PATENT APPLICATION

Conclusion

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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